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Copper-Catalyzed Synthesis of Quinazoline Derivatives via Ullmann-Type Coupling and Aerobic Oxidation

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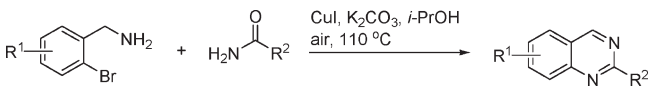

A simple and efficient copper-catalyzed approach to quinazoline derivatives has been developed, and the protocol uses readily available substituted (2-bromophenyl)-methylamines and amides as the starting materials, and the cascade reactions were performed under air via sequential Ullmann-type coupling and aerobic oxidation without addition of any ligand or additive. The present method provides a convenient and practical strategy for synthesis of quinazoline derivatives.

Quinazoline derivatives have attracted much attention for their various biological and medicinal properties. For example, they act as the potent tyrosine kinase and cellular phosphorylation inhibitors,[1] and they are also used as ligands for benzodiazepine and GABA receptors in the central nervous system (CNS)[2] or as DNA binders.[3] Some of them show remarkable activity as anticancer,[4] antiviral,[5] and antitubercular agents.[6] Molecules containing the quinazoline unit have been popular drugs. For example, Erlotinib is used in the treatment of several types of tumors,[7] Prazosin acts as an α-adrenergic blocker,[8] and Iressa as an epidermal growth factor receptor inhibitor was approved by the Food and Drug Administration in USA for the treatment of lung cancer[9] (Figure 1). Wide demands of diverse quinazoline derivatives in various fields promote people to develop different synthetic methods. Many methods for syntheses of quinazoline derivatives have been developed thus far.[10] For example, reactions of 2-amino-*N*-arylbenzamidines and formic acid provided 4-arylaminoquinazolines.[11] Reactions of 2-amino-*N*′-phenylbenzimidamides with aromatic aldehydes yielded 2-aryl-4-arylimino-2,3-dihydroquinazolines, followed by oxidation with potassium permanganate to give the corresponding quinazolines.[12] Couplings of 2-aminobenzonitriles with carbon dioxide (1 atm) at 20 °C, assisted by DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), gave 2,4-dihydroxyquinazolines.[13] 6-Substituted quinazoline-2,4-diones were converted to 2,4-dichloroquinazolines in excellent yields by refluxing in phosphorus oxychloride.[14] Although the previous methods for synthesis of quinazoline derivatives are efficient, the used starting materials often are not readily available and difficult to prepare. It is highly desirable to search for a more convenient and efficient approach. Recently, there has been great progress in copper-catalyzed *N*-arylations,[15] and the *N*-arylation strategy has been used to make *N*-heterocycles.[16] We have also developed some efficient methods for copper-catalyzed cross couplings[17] and synthesis of *N*-heterocycles.[18] Copper-catalyzed synthesis of quinazoline derivatives has also been developed by Truong's

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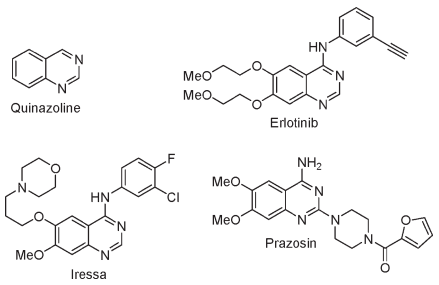
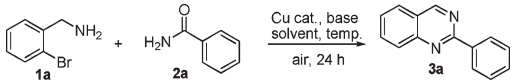


FIGURE 1. Quinazoline and popular drugs containing the quinazoline unit.

group[16g] and us[18b] via couplings of 2-halobenzaldehydes with amidine hydrochlorides. Considering more ready availability of amides than amidines, herein, we report a simple and efficient copper-catalyzed synthesis of quinazoline derivatives using inexpensive and readily available substituted (2-bromophenyl)methylamines and amides as the starting materials without addition of any ligand or additive under air.

During optimization of reaction conditions including the catalysts, bases and solvents, (2-bromophenyl)methylamine (**1a**) with benzamide (**2a**), were used as the model substrates. As shown in Table 1, four bases were investigated at 110 °C with 0.1 equiv of CuI as the catalyst (relative to amount of **1a**) in 2-propanol in a sealed vessel under air (entries 1−4), and K_2CO_3 showed the highest efficiency (entry 2). Several copper salts were tested, and CuI exhibited the best activity (compare entries 2 and 5−7). Only a trace amount of target product was observed in the absence of copper catalyst (entry 8). We attempted different solvents (entries 9−11), and 2-propanol gave the highest yield (compare entries 2 and 9−11). The yields decreased when reaction temperature was lowered (compare entries 2, 12, and 13). The cascade reaction afforded the target product in 20% yield under nitrogen atmosphere (extrusion of air), which showed oxygen in air involved in the oxidative process during the formation of the quinazoline derivative. However, only 32% yield was afforded when the reaction was performed in a flask linked with an opened condenser under air at the refluxing temperature of 2-propanol (83 °C) (entry 15). The result showed that lower temperature and more oxygen was not favorable for the Ullmann-type *N*-arylation (see the reaction mechanism in Scheme 1).

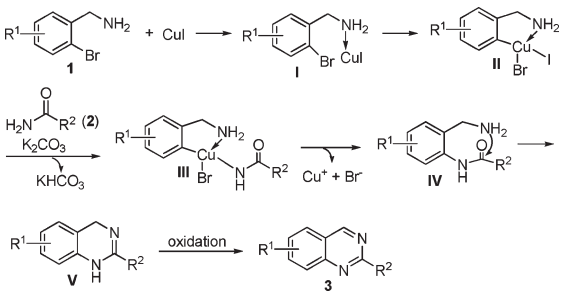
TABLE 1. Copper-Catalyzed Cascade Synthesis of 2-Phenylquinazoline (3a) via Reaction of (2-Bromophenyl)methylamine (1a) with Benzamide (2a): Optimization of Conditions[a]



entry	cat.	base	solvent	temp (°C)	yield (%)[b]
1	CuI	Cs_2CO_3	2-propanol	110	8
2	CuI	K_2CO_3	2-propanol	110	87
3	CuI	Na_2CO_3	2-propanol	110	46
4	CuI	K_3PO_4	2-propanol	110	43
5	CuBr	K_2CO_3	2-propanol	110	45
6	Cu_2O	K_2CO_3	2-propanol	110	29
7	$CuCl_2$	K_2CO_3	2-propanol	110	64
8		K_2CO_3	2-propanol	110	trace[c]
9	CuI	K_2CO_3	DMF	110	25
10	CuI	K_2CO_3	DMSO	110	33
11	CuI	K_2CO_3	dioxane	110	20
12	CuI	K_2CO_3	2-propanol	60	25
13	CuI	K_2CO_3	2-propanol	90	56
14	CuI	K_2CO_3	2-propanol	110	20[d]
15	CuI	K_2CO_3	2-propanol	83	32[e]

[a]Reaction condition: (2-bromophenyl)methylamine (**1a**) (0.3 mmol), benzamide (**2a**) (0.45 mmol), catalyst (0.03 mmol), base (0.6 mmol), solvent (1.0 mL) in a sealed vessel under air. [b]Isolated yield. [c]In the absence of copper catalyst. [d]Under nitrogen atmosphere. [e]In a flask linked with an opened condenser under air.

SCHEME 1. Possible Mechanism for Synthesis of Quinazoline Derivatives



The scope of copper-catalyzed cascade reactions of substituted (2-bromophenyl)methylamines and aromatic amides was investigated under the optimized conditions (10 mmol % CuI as the catalyst, 2 equiv of K_2CO_3 as the base, 2-propanol as the solvent under air). As shown in Table 2, all the substrates examined provided moderate to good yields at 110 °C. The substituted (2-bromophenyl)methylamines containing electron-donating groups showed slightly lower reactivity. For amides, the substrates containing electron-withdrawing groups usually provided higher yields than ones containing electron-donating groups. Unfortunately, couplings of the substituted (2-bromophenyl)methylamines with aliphatic amides did not work by

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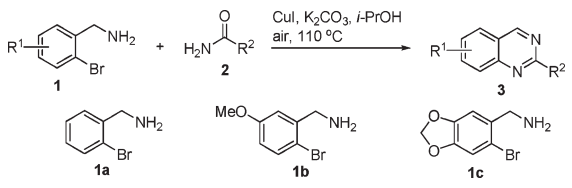
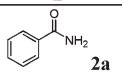
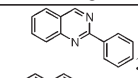
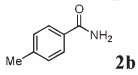
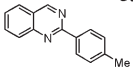
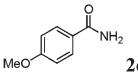
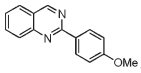
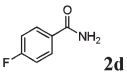
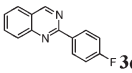
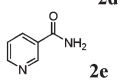
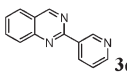
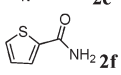
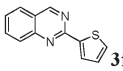
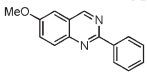
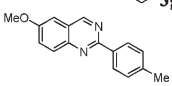
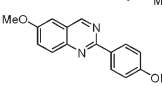
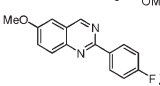
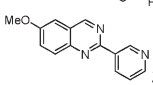
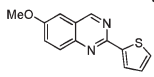
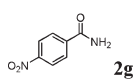
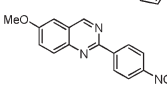
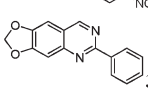
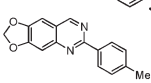
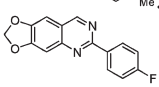
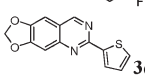
TABLE 2. Copper-Catalyzed Cascade Synthesis of Quinazoline Derivatives[a]



entry	2	3	yield[b]
1	 **2a**	 **3a**	87
2	 **2b**	 **3b**	62
3	 **2c**	 **3c**	54[c]
4	 **2d**	 **3d**	75[c]
5	 **2e**	 **3e**	64
6	 **2f**	 **3f**	73
7	**2a**	 **3g**	61
8	**2b**	 **3h**	61
9	**2c**	 **3i**	44
10	**2d**	 **3j**	53
11	**2e**	 **3k**	62
12	**2f**	 **3l**	69
13	 **2g**	 **3m**	52[c]
14	**2a**	 **3n**	64
15	**2b**	 **3o**	37[c]
16	**2d**	 **3p**	87
17	**2f**	 **3q**	61

[a]Reaction condition: substituted (2-bromophenyl)methylamine (**1**) (0.3 mmol), amide (**2**) (0.45 mmol), CuI (0.03 mmol), K_2CO_3 (0.6 mmol), 2-propanol (1.0 mL) under air, reaction temperature 110 °C, reaction time 24 h, in a sealed vessel. [b]Isolated yield. [c]Reaction time (32 h).

using a similar procedure. The cascade reactions could tolerate functional groups including the ether bond in the substituted (2-bromophenyl)methylamines (**1**), the C−F bond, nitro, ether bond and heterocycle in the aromatic amides (**2**).

A possible mechanism for synthesis of quinazoline derivatives was proposed in Scheme 1 according to the results above and the ortho-substituent effects.[18a,d,19] Coordination of substituted (2-bromophenyl)methylamine (**1**) with Cu(I) ion give **I**, and oxidative addition of **I** leads to **II**. Treatment of **II** with amide (**2**) provides **III** in the presence of base (K_2CO_3), and reductive elimination of **III** affords *N*-arylation product (**IV**) leaving copper catalyst. Intramolecular dehydrative cyclization in **IV** followed by air-promoted aromatization can be performed to provide the desired target product (**3**). The copper-catalyzed cascade reactions did not need a ligand because of the ortho-substituent effect of amino in substituted (2-bromophenyl)methylamine.

In summary, we have developed a simple and efficient method for synthesis of quinazoline derivatives. The protocol uses inexpensive and readily available substituted (2-bromophenyl)methylamines and amides as the starting materials without addition of any ligand or additive under air, the corresponding target products were obtained in moderate to good yields, and the cascade reactions underwent sequential Ullmann-type coupling and aerobic oxidation. The quinazoline derivatives are biologically and pharmaceutically active molecules; therefore, the present method will be of wide application in organic chemistry and medicinal chemistry.

Experimental Section

General Procedure for Synthesis of Compounds 3a−q. An oven-dried Schlenk tube was charged with CuI (6 mg, 0.03 mmol), potassium carbonate (83 mg, 0.6 mmol), amide (0.45 mmol), substituted (2-bromophenyl)methylamine (0.3 mmol), and *i*-PrOH (1.0 mL). The tube was sealed, and the mixture was stirred at 110 °C for 24−32 h. After the resulting solution was cooled to room temperature, the solvent was removed, and the residue was purified by silica gel column chromatography to give the desired product. Two examples are shown as follows:

2-(Thiophen-2-yl)quinazoline (3f). Eluent: petroleum ether/ethyl acetate (10:1). Yield: 46 mg (73%). White solid, mp 132−134 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.33 (s, 1H), 8.15−8.14 (m, 1H), 7.99 (d, J = 6.9 Hz, 1H), 7.86−7.84 (m, 2H), 7.54−7.49 (m, 2H), 7.18 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 160.7, 158.1, 150.8, 144.1, 134.6, 130.2, 129.5, 128.6, 128.4, 127.5, 127.2, 123.6. HR-MS $[M + H]^+$ m/z calcd for $C_{12}H_8N_2S$ 213.0486, found 213.0487.

6-(4-Fluorophenyl)-[1,3]dioxolo[4,5-*g*]quinazoline (3p). Eluent: petroleum ether/ethyl acetate (10:1). Yield 70 mg (87%). White solid, mp 216−218 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.13 (s, br, 1H), 8.56−8.51 (t, 2H), 7.29 (s, 1H), 7.20−7.17 (m, 2H), 7.09 (s, 1H), 6.14 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 165.5, 163.9, 157.6, 154.5, 148.6, 134.6, 130.6, 130.5, 130.4, 120.9, 115.9, 115.7, 115.6, 105.1, 102.5, 102.2, 102.0. HR-MS $[M + H]^+$ m/z calcd for $C_{15}H_9FN_2O_2$ 269.0726, found 269.0728.

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Supporting Information Available: General experimental procedures, characterization data, and ^{1}H, ^{13}C NMR spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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